As explained in the specification, the structures represented by Formula I (A, B and C) are planar and potentially aromatic, while those represented by Formula II are puckered and non-aromatic. This means that the mechanism of action of the two types of compounds are clearly distinguished by their significant structural differences, although both, in their own manner, exhibit viral, bacterial, parasitic, or cancer inhibition.

For example, the **planar** compounds of Formula I have significantly greater chance of being incorporated into viral or bacterial DNA by polymerases, and consequently terminate the transcription (and hence the replication) process by causing considerable DNA distortion as illustrated in Figs 1, 2A, 2B, and 2C of '310.

In contrast, the **non-planar** ring structures of Formulas II-IV are highly unlikely to be recognized and accepted as viable substrates by the host, viral, or bacterial polymerases for several reasons, including:

(a) the heterocyclic base moieties of all natural nucleotide substrates are planar and aromatic,

(b) with a puckered structure, it is difficult to form proper base-pairing with a complementary nucleotide of the opposite DNA/RNA strand, and

(c) the puckered structure would also seriously interfere with the DNA/RNA stabilizing stacking interactions.

Hence, even the error-prone viral and bacterial polymerases are unlikely to accept these non-planar nucleotide analogues as substrates. However, these non-planar molecules can still inhibit the replication process by directly binding to an allosteric site of either a transcriptase or a replicase by causing severe conformation distortion at the enzyme active site such as the natural substrate binding site of a

polymerase. Therefore, while the mechanisms of action of the planar and non-planar compounds are totally different, the end result of inhibiting e.g., the viral or bacterial replication is the same.

Further, by alternative action, the planar and non-planar RENs (Ring Expanded Nucleosides and Nucleotides) bind to two totally different enzymes: for example, the planar REN binding to adenosine deaminase (ADA) as a substrate, and the non-planar REN binding to guanine deaminase (or guanase) as an inhibitor.

In the first case, the **planar** REN will compete as an antimetabolite with the enzyme ADA's natural substrate adenosine/deoxyadenosine, which is also planar, for the enzyme active site and hinder its binding, which in turn results in the accumulation of the cytotoxic adenosine/deoxyadenosine in the cell. The accumulated adenosine-5'-triphosphate (or deoxyadenosine-5'-triphosphate) in the cell acts as a feedback inhibitor of the key enzyme ribonucleotide reductase involved in the *de novo* biosynthesis of deoxynucleotides that are necessary for DNA synthesis. The net outcome is the inhibition of cancer (or viral) growth.

In contrast, the **non-planar** REN, with a molecular structure similar to that of the non-planar azepinomycin, a natural inhibitor of guanase represented in Figure 3C of '310, may bind to guanase. The latter is an enzyme involved in the *salvage* pathway of biosynthesis of nucleotides, which is especially pronounced in cancerous cells. Thus, the non-planar RENs or their heterocyclic bases may specifically inhibit the DNA replication in tumor cells without seriously affecting the normal cells. Therefore, although the binding modes (substrate *versus* inhibitor) as well as the enzymes involved (adenosine deaminase *versus* guanase) in the planar *versus* non-

planar RENs are totally different, the end result of inhibiting the tumor growth is the same.

Finally, in some cases, the mechanisms of molecular actions as well as the end results of planar and non-planar RENS may be distinctly different, for example, one resulting in the antiviral action and the other affecting the tumor growth.

Accordingly, the molecular structures of planar and non-planar RENs are distinctly different. They have totally different 3-D structures or stereochemistry and are anticipated to bind quite differently at an enzyme's active or allosteric site, and even more likely, they may bind to different enzymes altogether. The end results may be same or different depending upon what enzymes or receptors are being targeted.

In view of the above, the applicants submit that the presently claimed invention is not obvious in view of the claims of the '310 patent.

The applicants respectfully traverse the rejection of claims 24-69 under 35 USC 102(e) in view of Hosmane et al. ,USP 5,843,912 ('912). This reference does not anticipate the presently claimed invention or make it obvious.

While the '912 patent discloses the compounds of Formulas II, III and IV that are employed in the presently claimed methods of treatment, the presently claimed methods recited features and are supported by investigations and experiments performed after the '912 patent was filed. The presently claimed methods could not have been anticipated or found to be obvious by a person of ordinary skill in the art, based upon the teachings of '912.

For example, as explain above, the non-planar ring structures of Formulas II-IV are highly unlikely to be recognized and accepted as viable substrates by the host, viral, or bacterial polymerases for several reasons, including:

(a) the heterocyclic base moieties of all natural nucleotide substrates are planar and aromatic,

(b) with a puckered structure, it is difficult to form proper base-pairing with a complementary nucleotide of the opposite DNA/RNA strand, and

(c) the puckered structure would also seriously interfere with the DNA/RNA stabilizing stacking interactions.

Thus, even the error-prone viral and bacterial polymerases are unlikely to accept these non-planar nucleotide analogues as substrates. However, these non-planar molecules can still inhibit the replication process by directly binding to an allosteric site of either a transcriptase or a replicase by causing severe conformation distortion at the enzyme active site such as the natural substrate binding site of a polymerase. Such supporting means of treatment are nowhere disclosed or suggested in the '912 patent.

Further, by alternative action, the compounds of Formulas II, III and IV, may bind to guanase. The latter is an enzyme involved in the *salvage* pathway of biosynthesis of nucleotides, which is especially pronounced in cancerous cells. Thus, these compounds or their heterocyclic bases may specifically inhibit the DNA replication in tumor cells without seriously affecting the normal cells. Such means of treatment are nowhere disclosed or suggested in the '912 patent.

Accordingly, the applicants submit that the presently claimed methods are nowhere disclosed, suggested or made obvious by the teachings of '912. The

presently claimed methods are not only allowable under Section 102 but are also allowable under Section 103.

The applicants observed that the two previously submitted PTO Forms 1449 (dated October 7, 2003) listing references cited in the parent application 09/295,303 were not considered because the Examiner found the print to be unclear. The applicants apologize for the lines of the Forms obscuring some of the print. The two sheets of Forms PTO 1449 with fully legible print, are herewith resubmitted as enclosed with this Response. Official entry and consideration are respectfully requested. Please return a copies with the Examiner's initials in the left column per MPEP 609.

In view of the above, it is believed that this application is in condition for allowance and a Notice to that effect is requested.

Respectfully submitted,

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